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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARTON, Linda, S.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **DODSON, Jason, W.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **GAITANOPOULOS, Dimitri, E.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **GIRARD, Gerald, R.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **KING, Bryan, W.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **MCATEE, John, Jeffrey** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). **NEEB, Michael, J.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US).

(74) Agent: **HALL, Linda, E.**; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

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SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas & Ohlstein (2000). Trends Cardiovasc. Med., 10(6):229-37)

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: **131; 10-12**) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypersensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al.Brain Research* 923 (2001) 120-127.

Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

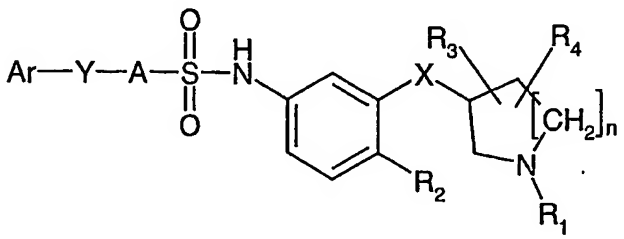
In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

Ar is phenyl, pyridinyl, thienyl, furanyl, oxazoyl, pyrroyl, triazinyl, imidazoyl, pyrimidinyl, pyrazinyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl, naphthyl, quinolinyl, naphthyridinyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, azaspirononoyl, benothiophenyl, substituted or unsubstituted by one, two, three, or four of the following: halogen, CN, $S(O)_p(C_{1-6}$ alkyl), CF_3, OCF_3, SCF_3, C_{1-6} alkyl, Ph, OH, C_{1-6} alkoxy, COR_{11}, CO_2H, $CO_2(C_{1-6}$ alkyl), NR_5R_6, NR_5COR_{13}, $NR_5SO_2R_{13}$, $CONR_7R_8$, NO_2, C_{1-3} alkylenedioxy, $CH_2NR_7R_8$, or CH_2OR_{11};

A is phenyl, pyridyl, thienyl, furanyl, , oxazoyl, pyrroyl, triazinyl, imidazoyl, pyrimidinyl, pyrazinyl, N-phenylpyrroyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl, naphthyl, indoyl, quinolinyl, quinazolinyl, naphthyridinyl, benzothiophenyl, benzofuranyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, benzothiazoyl, benzoxazoyl, benzothiadiazoyl, benzoxadiazoyl, or benzimidazoyl, all of which may be substituted or unsubstituted by one, two, three or four halogens, C_{1-6} alkyl, C_{1-6} alkoxy, $CO_2(C_{1-6}$ alkyl), CN, CF_3 or NO_2 groups;

Y is O, NH, $-C(O)-NH-CH_2-$, $-S(O_p)-$, CH_2, or a bond;

R_1 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_mR_{14}$;

R_2 is hydrogen, halogen, CF_3, CN, or C_{1-4} alkyl;

R_3 and R_4, are independently hydrogen, C_{1-6} alkyl, benzyl, $-C(R_{13})_2-OR_{11}$, $-COOR_{12}$, $-CONR_{11}$, or $-C(R_{13})_2-N(R_{11})_2$;

R_5, R_6, R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_{11} is hydrogen or C_{1-6} alkyl;

R_{12} is C_{1-6} alkyl;

R_{13} is independently hydrogen or C_{1-3}alkyl;

R_{14} is phenyl, OH, or $-(C=O)C_{1-3}$alkyl;

X is O, S, or CH_2;

n is 0, 1 or 2;

m is 1 or 2;

p is 0, 1, or 2

provided that when R_{14} is OH, m is 2;

also provided that when A is thienyl, and Ar is phenyl, pyrazoyl, napthyl, quinolinyl, benzodioxoyl, or benzofuranyl, Y is not a bond;

also provided that when A is phenyl and Y is a bond, Ar is attached ortho to SO_2-;

also provided that when Ar is phenyl, A is not pyridyl;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo, and iodo, respectively.

Ar is preferably phenyl, pyridinyl, thienyl, furanyl, oxazoyl, pyrroyl, imidazoyl, pyrimidinyl, pyrazoyl, substituted or unsubstituted by one, two, or three of the following: Cl, Br, F, CN, $S(O)_p(C_{1-3}$ alkyl), CF_3, C_{1-6} alkyl, OH, C_{1-3} alkoxy, COR_{11}, NR_5R_6, NR_5COR_{13}, $CONR_7R_8$, or NO_2.

A is preferably phenyl, pyridyl, thienyl, furanyl, , oxazoyl, imadazolyl, pyrimidinyl, pyrazoyl, thiazoyl, all of which may be substituted or unsubstituted by one or two Cl, Br, F, C_{1-3} alkyl, C_{1-3} alkoxy, CN, CF_3 or NO_2 groups.

Y is preferably O, NH, $-S(O_p)-$, CH_2, or a bond.

R_1 is preferably hydrogen or C_{1-3} alkyl.

R_2 is preferably hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl.

R_3 and R_4, are preferably hydrogen or C_{1-3} alkyl.

R_5, R_6, R_7, and R_8 are preferably hydrogen or C_{1-3} alkyl.

R_{11} is preferably hydrogen or C_{1-3} alkyl.

R_{13} is preferably hydrogen or C_{1-3}alkyl.

X is preferably O.

n is preferably 1.

p is preferably 0, 1 or 2.

Preferred compounds are :

4-(2-chlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

3-(3,5-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(phenylsulfonyl)-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(phenylsulfonyl)-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)-2-pyridinyl]sulfonyl}-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)-4-{[4-(trifluoromethyl)phenyl]oxy}benzenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(phenyloxy)-3-(trifluoromethyl)benzenesulfonamide;

4-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(2-naphthylthio)benzenesulfonamide;

2-chloro-4-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(4-fluorophenyl)thio]benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(methyloxy)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(3-chloro-4-fluorophenyl)thio]-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide;

2-chloro-4-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-phenoxybenzenesulfonamide; MS (ES) m/e 527

3-chloro-4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide

3-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

3-chloro-4-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

3-chloro-4-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-{4-[2-chloro-4-({[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenoxy]phenyl}acetamide;

5-bromo-6-[(3,5-dichlorophenyl)amino]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]pyridine-3-sulfonamide;

6-{[2,3-bis(methyloxy)phenyl]amino}-5-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-pyridinesulfonamide;

3-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)-3-[3-(trifluoromethyl)phenoxy]benzenesulfonamide;

4-{[2-chloro-3-(trifluoromethyl)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-{[2-fluoro-3-(trifluoromethyl)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-(3,5-Dichlorophenoxy)-3-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

4-bromo-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(2-naphthalenylthio)-2-thiophenesulfonamide;

5-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(2-naphthalenylthio)-2-thiophenesulfonamide;

4-bromo-5-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide;

5-{[3,4-bis(methyloxy)phenyl]thio}-4-bromo-2-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide;

3-bromo-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(3,5-dichlorophenyl)thio]-2-thiophenesulfonamide;

4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(4-fluorophenyl)thio]-2-thiophenesulfonamide;

5-[(3-chloro-4-fluorophenyl)thio]-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-thiophenesulfonamide;

5-{[3,4-bis(methyloxy)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(phenyloxy)-2-thiophenesulfonamide;

4-{[5-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-nitro-2-thienyl]amino}benzamide;

5-[(3-methylphenyl)amino]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2',4,5-tris(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3',5'-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

2-(1-benzothien-7-yl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(trifluoromethyl)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2',4'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

2,5-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(3-thienyl)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4'-dimethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3'-amino-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-methyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-[(trifluoromethyl)oxy]-2-biphenylsulfonamide;

3'-(aminomethyl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(2-naphthalenyl)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-[(methylsulfonyl)amino]-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-1,1':3',1"-terphenyl-2-sulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-formyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

2-(1,3-benzodioxol-5-yl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-ethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(methylthio)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-formyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-1,1':4',1"-terphenyl-2-sulfonamide;

4'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-cyano-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(methylsulfonyl)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,4',5-tris(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',5'-dimethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3',5'-bis(trifluoromethyl)-2-biphenylsulfonamide; and

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(1-naphthalenyl)benzenesulfonamide.

More preferred compounds are:

4-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(2-chlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(3,5-dichlorophenyl)thio] benzenesulfonamide;

4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

3-chloro-4-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

methyl 4-[2-chloro-4-({[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenoxy]benzoate;

methyl 3-{[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]oxy}benzoate;

3-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

3-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

3-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

3-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

2-bromo-5-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

4-bromo-5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-2-chloro-5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide;

4-bromo-2-chloro-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide;

5-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[4-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide;

4-bromo-5-{[3-(methyloxy)phenyl]thio}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-{[3,4-bis(methyloxy)phenyl]thio}-4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-chloro-3-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(3-fluorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide;

N-[4-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-3-(trifluoromethyl)phenyl]-4-nitro-5-(phenylamino)-2-thiophenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-cyano-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-(trifluoromethyl)-2-biphenylsulfonamide;

3'-cyano-4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-biphenylsulfonamide;

4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3'-(trifluoromethyl)-2-biphenylsulfonamide;;

3',5'-dichloro-4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-biphenylsulfonamide;

3'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-methyl-4,5-bis(methyloxy)-3'-nitro-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4,4',5-tetrakis(methyloxy)-2-biphenylsulfonamide;

3',4'-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-nitro-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4,5-tris(methyloxy)-2-biphenylsulfonamide;

3'-acetyl-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

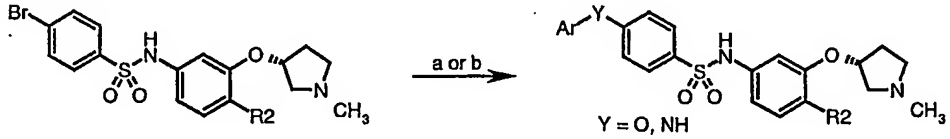
3'-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide; and

4'-acetyl-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Compounds of Formula (I) may be prepared as outlined in Schemes 1 - 9. Starting compounds 1 may be prepared as outlined in WO 289793, incorporated by reference herein.

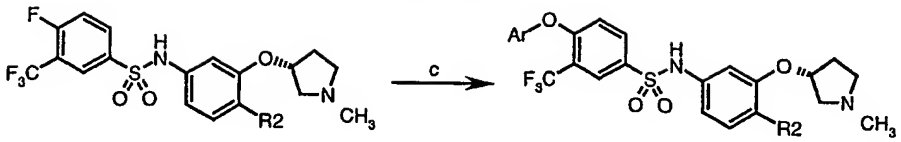
Scheme 1



1 2

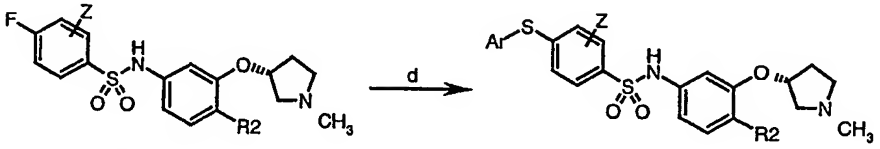
a) phenol or anline, 2-biphenylyl[bis(1,1-dimethylethyl)]phosphine, palladium acetate, potassium phosphate b) 2-biphenylyl(dicyclohexyl)phosphine, tris(dibenzylideneacetone)dipalladium, potassium phosphate

Scheme 2



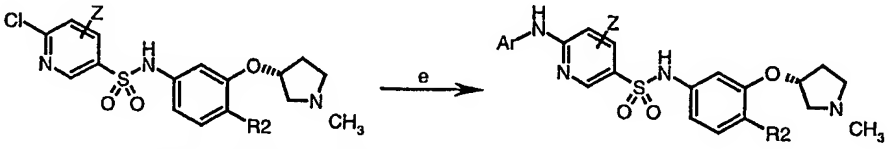
c) Phenol, NaH, DMF

Scheme 3



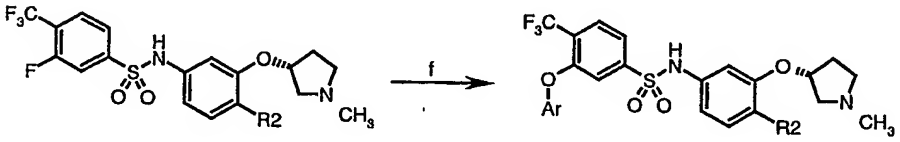
d) thiophenol, 1N NaOH, DMF, heat (Z is any listed substuient for A)

Scheme 4



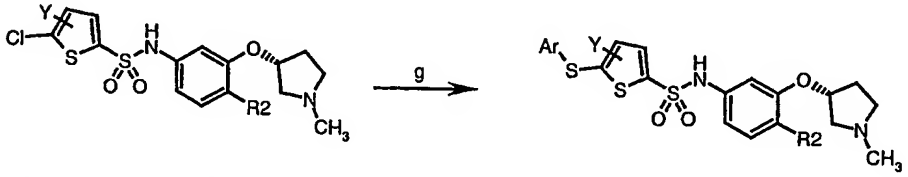
e) anline, 4M HCl, DME, heat (Z is any listed substuient for A)

Scheme 5



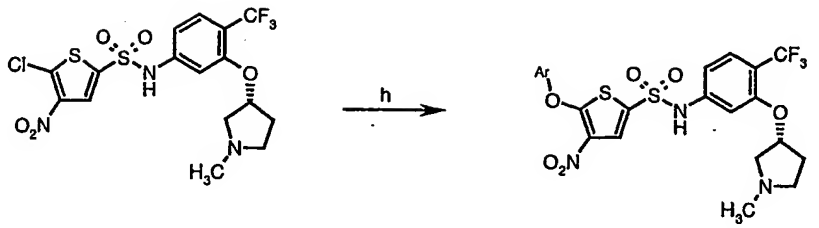
f) NaH, Cs_2CO_3, phenol, heat

Scheme 6



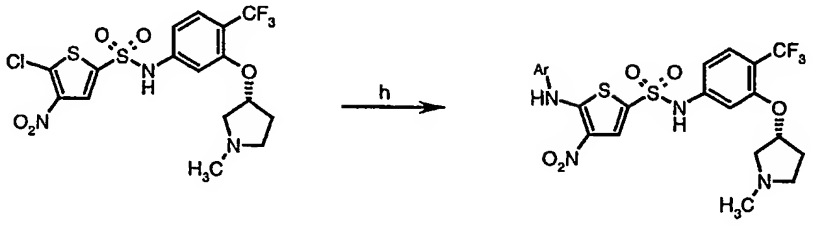
g) thiophenol, NaOH, DMF, heat (Y is any listed substuient for A)

Scheme 7



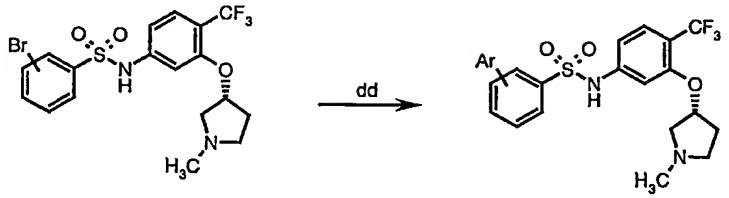
h) cesium carbonate, phenol, DMF, rt.

Scheme 8



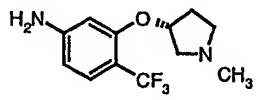
j) aniline, DMF, micro-wave heating.

Scheme 9

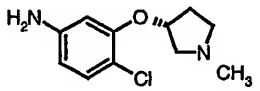


k) dppfPdCl$_2$, DMF, potassium carbonate, arylboronic acid , microwave heating.

Anilines **A** and **B** have been previously described: WO 2002089792 A1, incorporated by reference herein.



Aniline **A**



Anline **B**

Sulfonyl chlorides, when not commercially available, can prepared by methods known in the art: Shahripour, A.B. et al. *Bioorg. Med. Chem.* **2002**, *10*, 31; Cross, P.E. et al. *J. Med. Chem.* **1978**, *21*, 845; Huntress et al *J. Amer. Chem. Soc.* **1941**, *63*, 3446; Hashimoto, H. et al *J.*

Med. Chem. **2002**, *45*, 1511; O'Brien, P. M. et al. *J.Med.Chem.* **2000**, *43*, 156; Brundish, D. *J.Med.Chem.* **1999**, *22*, 4584.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a

binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate

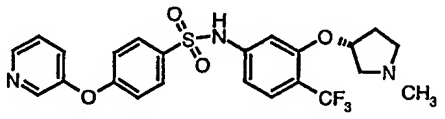
was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 1 nM – 1000 nM.

The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

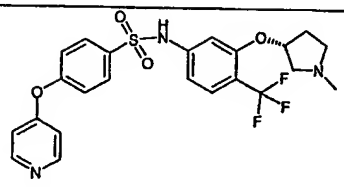
N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(pyridin-3-yloxy)benzenesulfonamide

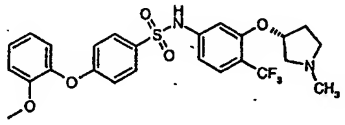
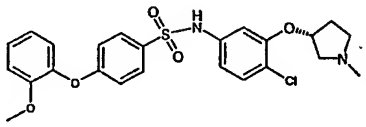
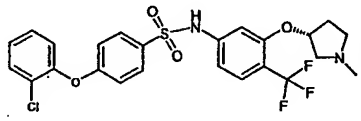
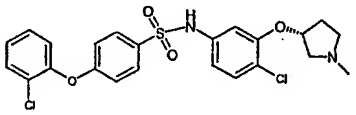
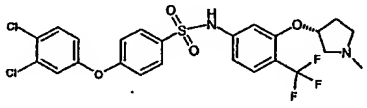
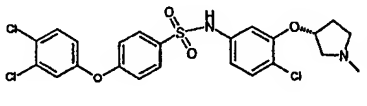
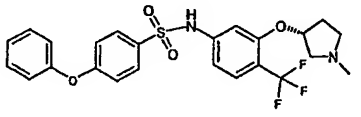


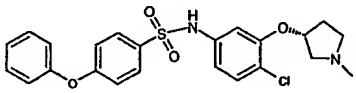
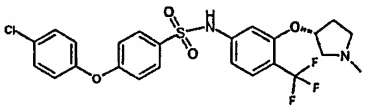
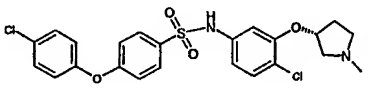
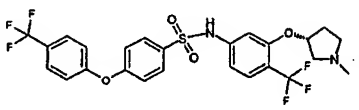
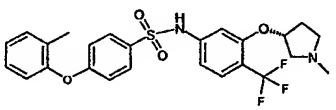
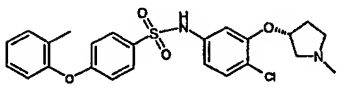
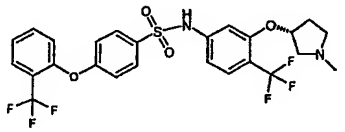
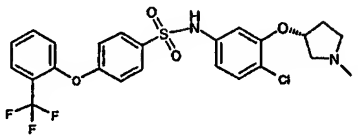
Aniline A (39 mg, 0.15 mmol) was dissolved in 1 mL of methylene chloride and treated with 4-(3-pyridinyloxy)benzenesulfonyl chloride (55.1 mg, 0.18 mmol) and pyridine (0.024 mL, 0.30 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 1 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 12 min, UV detection at 214 nm) to give 31.3 mg (42%) of the title compound as a tan oil. MS (ES) m/e 494.0 $[M+H]^+$

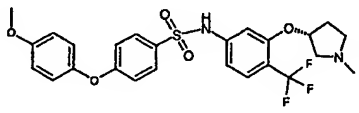
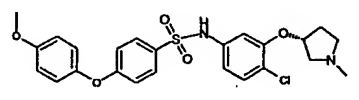
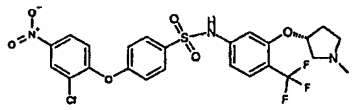
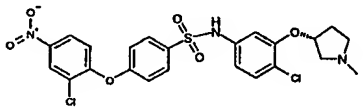
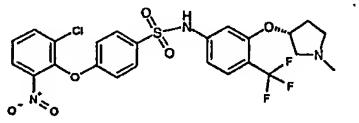
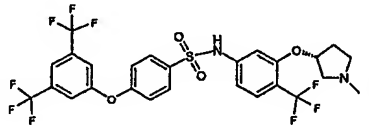
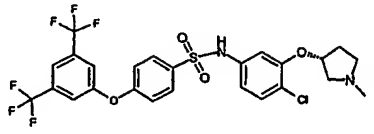
Examples 2-40

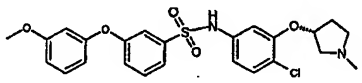
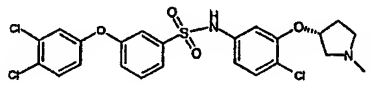
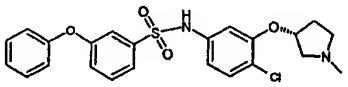
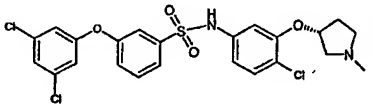
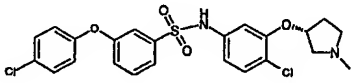
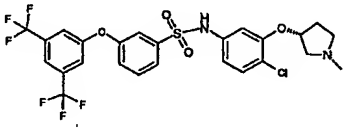
The following examples were prepared according to the representative procedure in Example 1 using the appropriate sulfonyl chlorides as starting material, in some cases using acetonitrile rather than methylene chloride as the solvent, and in some cases also substituting Aniline **B** for Aniline A.

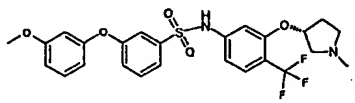
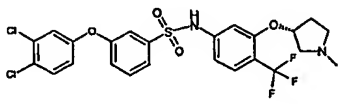
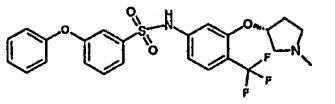
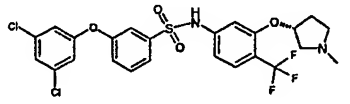
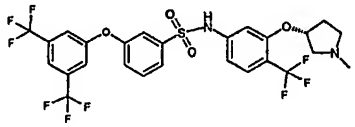
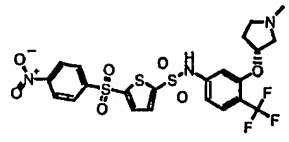
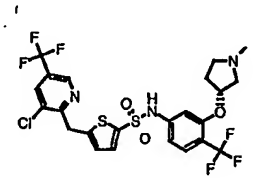
#	structure	name	m/z
2		N-[3-((R)-1-Methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4-(pyridin-4-yloxy)-benzenesulfonamide	494

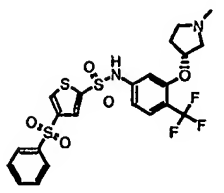
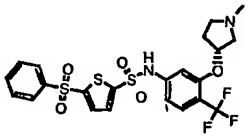
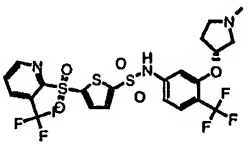
3		4-(2-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	523
4		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(2-methoxyphenoxy)benzenesulfonamide	489
5		4-(2-chlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	527
6		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(2-chlorophenoxy)benzenesulfonamide	493
7		4-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	561
8		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(3,4-dichlorophenoxy)benzenesulfonamide	527
9		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-phenoxybenzenesulfonamide	493

10		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-phenoxybenzenesulfonamide	459
11		4-(4-chlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	527
12		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(4-chlorophenoxy)benzenesulfonamide	493
13		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-[4-(trifluoromethyl)phenoxy]benzenesulfonamide	561
14		4-(2-methylphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	507
15		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(2-methylphenoxy)benzenesulfonamide	473
16		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-[2-(trifluoromethyl)phenoxy]benzenesulfonamide	561
17		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-[2-(trifluoromethyl)phenoxy]benzenesulfonamide	527

18		4-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	523
19		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(4-methoxyphenoxy)benzenesulfonamide	489
20		3,5-dichloro-4-(2-chloro-4-nitrophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	642
21		3,5-dichloro-N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4-(2-chloro-4-nitrophenoxy)benzenesulfonamide	607
22		4-(2-chloro-6-nitrophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	572
23		4-[3,5-bis(trifluoromethyl)phenoxy]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	629
24		4-[3,5-bis(trifluoromethyl)phenoxy]-N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-	595

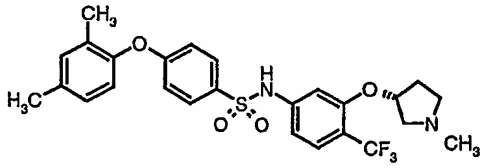
		yl]oxy}phenyl)benzenesulfonamide	
25		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-3-(3-methoxyphenoxy)benzenesulfonamide	489
26		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-3-(3,4-dichlorophenoxy)benzenesulfonamide	529
27		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-3-phenoxybenzenesulfonamide	459
28		N-(4-chloro-3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}phenyl)-3-(3,5-dichlorophenoxy)benzenesulfonamide	527
29		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-[(4-chlorophenyl)oxy]benzenesulfonamide	493
30		3-{[3,5-bis(trifluoromethyl)phenyl]oxy}-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	595

31		3-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	523
32		3-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	561
33		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-3-phenoxybenzenesulfonamide	493
34		3-(3,5-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	561
35		3-[3,5-bis(trifluoromethyl)phenoxy]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	629
36		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-[(4-nitrophenyl)sulfonyl]-2-thiophenesulfonamide	593.0
37		5-{[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	599.8

38		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(phenylsulfonyl)-2-thiophenesulfonamide	546.6
39		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(phenylsulfonyl)-2-thiophenesulfonamide	546.6
40		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)-2-pyridinyl]sulfonyl}-2-thiophenesulfonamide	616.0

Example 41

4-(2,4-dimethylphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide

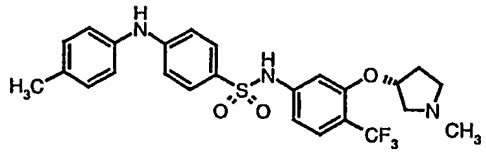


4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl] benzenesulfonamide (50 mg, 0.104 mmol) was added to an oven-dried, argon-charged conical-bottom vial with a teflon coated septum along with 2,4-dimethylphenol (12.6 uL, 0.104 mmol), 2-biphenylyl[bis(1,1-dimethylethyl)]phosphine (0.9 mg, 3.12 umol), palladium acetate (0.47 mg, , 2.08 umol), and potassium phosphate (36.9 mg, 0.174 mmol). Toluene (0.5 mL) was added and stirred, and the suspension was heated to 100 °C and maintained at this temperature for 18 hours. The solvent was removed via evaporation with a stream of nitrogen gas, and the residue was dissolved in 1 mL of DMSO, filtered through a 0.2 micron Acrodisk, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B:

water, A: 5% to 95% during 20 min, UV detection at 214 nm) to give 11.7 mg (22%) of the title compound as a colorless film. MS (ES) m/e 521 $[M+H]^+$

Example 42

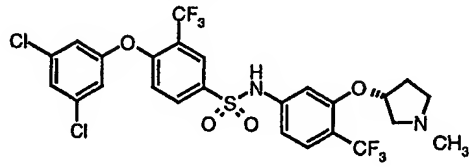
4-[(4-methylphenyl)amino]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide



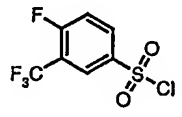
4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl] benzenesulfonamide (50 mg, 0.104 mmol) was added to an oven-dried, argon-charged conical-bottom vial with a teflon coated septum along with p-toluidine (11.1 mg, 0.104 mmol), 2-biphenylyl(dicyclohexyl)phosphine (0.73 mg, 2.08 umol), tris(dibenzylideneacetone)dipalladium (palladium-DBA) (0.95 mg,, 1.04 umol), and potassium phosphate (36.9 mg, 0.174 mmol). Toluene (0.5 mL) was added and stirred, and the suspension was heated to 100 °C and maintained at this temperature for 18 hours. The solvent was removed via evaporation with a stream of nitrogen gas, and the residue was dissolved in 1 mL of DMSO, filtered through a 0.2 micron Acrodisk, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 20 min, UV detection at 214 nm) to give 11.2 mg (21%) of the title compound as a colorless film. MS (ES) m/e 506 $[M+H]^+$

Example 43

4-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide

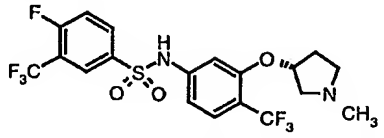


a) 4-fluoro-3-(trifluoromethyl)benzenesulfonyl chloride



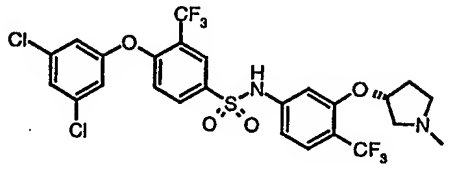
4-fluoro-3-(trifluoromethyl)aniline (1.40 g, 7.82 mmol) was dissolved in 3 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 1.53 mL, 11.7 mmol) and *tert*-butyl nitrite (1.39 mL, 11.7 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (1.16 g, 11.7 mmol) in 9 mL of glacial acetic acid at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 200 mL of an ice/water slurry. The aqueous suspension was extracted with ether (2 x 200 mL) and the combined organic layers were washed twice with water (400 mL), washed once with saturated NaCl (400 mL), dried over sodium sulfate, filtered, and concentrated to 1.9 g (93 %) of an orange oil which was used directly in the next step without further purification.

b) 4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide



Aniline A (1.00 g, 3.84 mmol) was dissolved in 30 mL of acetonitrile and treated with 4-fluoro-3-(trifluoromethyl)benzenesulfonyl chloride (1.9 g, 7.23 mmol) and pyridine (1.24 mL, 15.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 5 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 50 mm, 50 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 1.04 g (56%) of the title compound as a yellow foam. MS (ES) m/e 487 $[M+H]^+$.

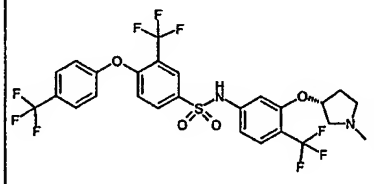
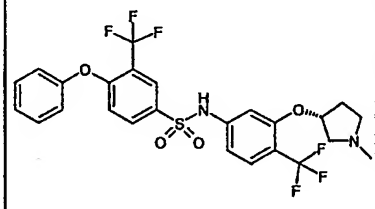
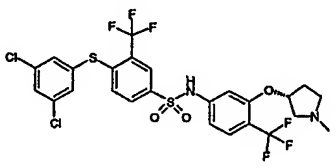
c) 4-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide

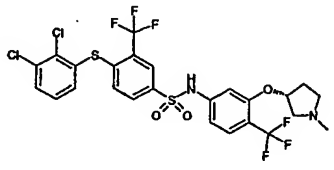
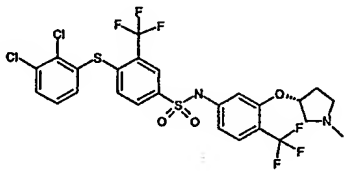


3,5-Dichlorophenol (40.0 mg, 0.246 mmol) was dissolved in 1 mL of anhydrous DMF and treated with NaH (60 % dispersion in mineral oil, 13.2 mg, 0.328 mmol). After all bubbling had stopped, the reaction was stirred for an additional 30 minutes and treated with a solution of 4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3 (trifluoromethyl) benzene sulfonamide (80.0 mg, 0.164 mmol) in 0.5 mL of anhydrous DMF. The reaction was heated at 70 °C for four hours, then at 105 °C for five hours, and then treated again with 3,5-dichlorophenol (133.7 mg, 0.82 mmol), NaH (60 % dispersion in mineral oil, 33.0 mg, 0.82 mmol) and calcium carbonate (82.1 mg, 0.82 mmol). The reaction was heated for an additional 3 hours at 105 °C, filtered through a 0.2 micron Acrodisk, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 32.0 mg (31%) of the title compound as a tan solid. MS (ES) m/e 629 $[M+H]^+$

Examples 44-49

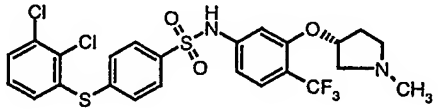
The following compounds were prepared by a method similar to the one described in Example 44 using the appropriate phenols or benzenethiols in place of 3,5-dichlorophenol.

#	Chemical Structure	Compound Name	m/z
44		4-[(2-chlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide	595
45		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)-4-{[4-(trifluoromethyl)phenyl]oxy}benzenesulfonamide	629
46		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(phenyloxy)-3-(trifluoromethyl)benzenesulfonamid	561

		e	
47		4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide	645
48		4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide	645

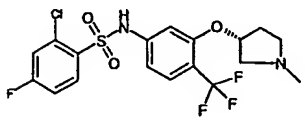
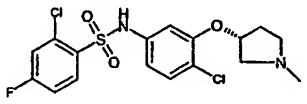
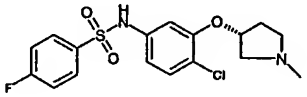
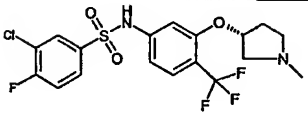
Example 49

4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide



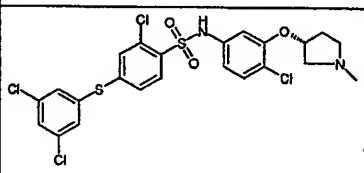
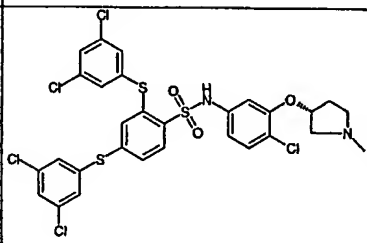
4-fluoro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl] benzenesulfonamide (209 mg, 0.500 mmol) was added to a thoroughly mixed and vigorously stirred mixture of 2,3-dichlorothiophenol (98.5 mg, 0.55 mmol), 1N NaOH (0.550 mL, 0.550 mmol), and 3 mL of DMF and heated to 100 °C for 8 hours. The reaction was allowed to cool to room temperature, was filtered, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 42.0 mg (15%) of the title compound as an amber microcrystalline solid. MS (ES) m/e 577 [M+H]+

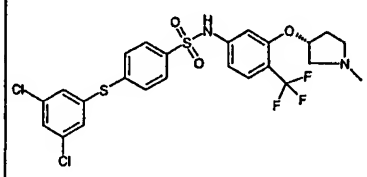
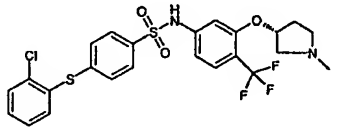
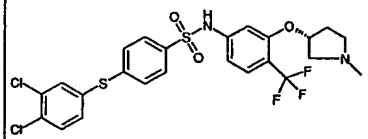
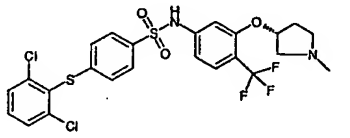
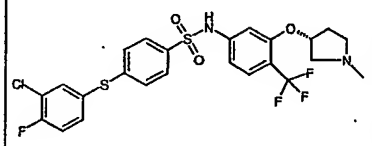
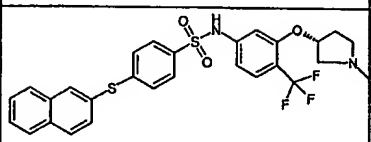
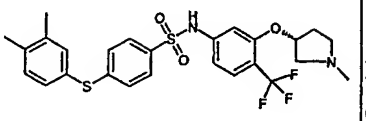
4-Fluorobenzenesulfonamides substituted for 4-fluoro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl] benzenesulfonamide:

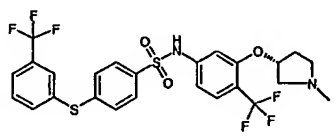
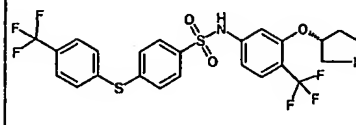
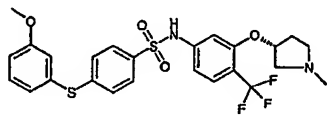
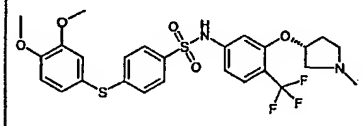
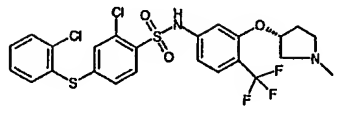
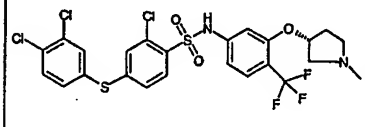
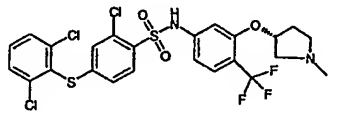
4-Fluorobenzene Sulfonamide	Compound Name
	2-chloro-4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide
	2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-fluorobenzenesulfonamide
	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-fluorobenzenesulfonamide
	3-chloro-4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide

Examples 50-105

The following compounds were prepared according to a procedure similar to the one described in Example 50, except substituting the appropriate phenol or benzenethiol for 2,3-dichlorothiophenol, and sometimes substituting the appropriate 4-fluorobenzenesulfonamide from the table above for 4-fluoro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl] benzenesulfonamide:

#	structure	name	m/z
50		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(3,5-dichlorophenyl)thio] benzenesulfonamide	577
51		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,4-bis[(3,5-dichlorophenyl)thio] benzenesulfonamide	719

52		4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	577
53[1]		4-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	543
54		4-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	577
55		4-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	577
56		4-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	561
57		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(2-naphthylthio)benzenesulfonamide	559
58		4-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	537

59		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide	577
60		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide	577
61		4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	539
62		4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	569
63		2-chloro-4-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	577
64		2-chloro-4-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	611
65		2-chloro-4-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulf	611

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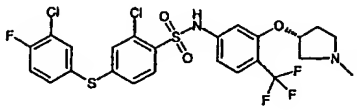
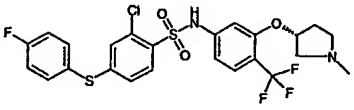
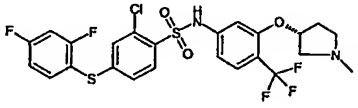
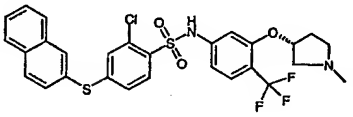
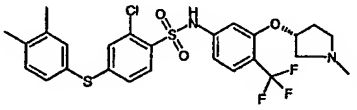
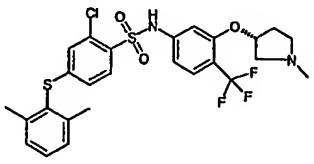
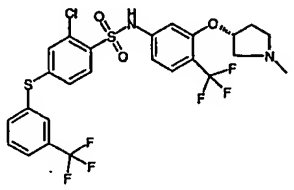
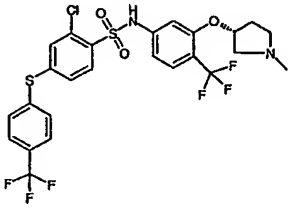
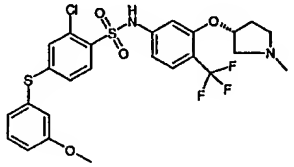
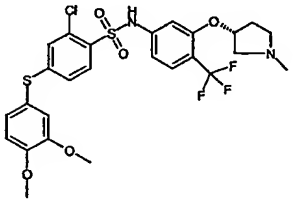
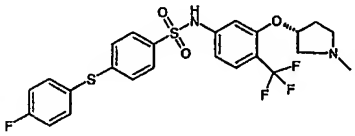
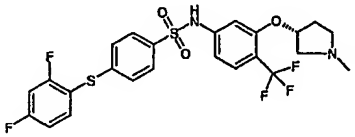
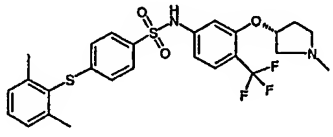
66		2-chloro-4-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	595
67		2-chloro-4-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	561
68		2-chloro-4-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	579
69		2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(2-naphthylthio)benzenesulfonamide	593
70		2-chloro-4-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	571
71		2-chloro-4-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	571

72		2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide	611
73		2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide	611
74		2-chloro-4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	573
75		2-chloro-4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	603
76		4-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	527
77		4-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	545
78		4-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulf	537

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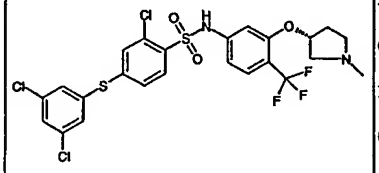
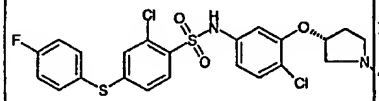
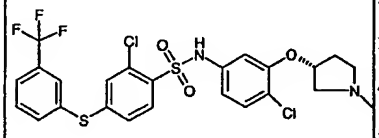
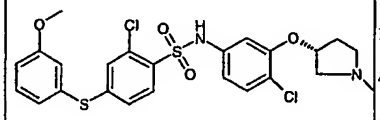
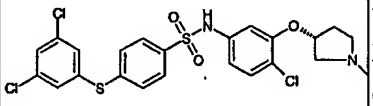
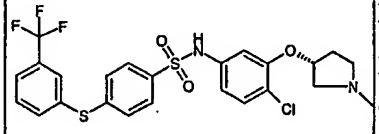
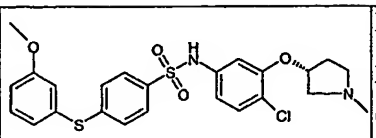
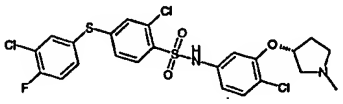
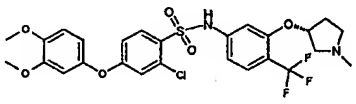
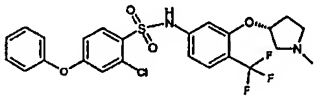
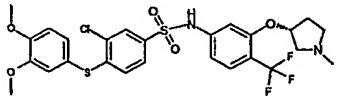
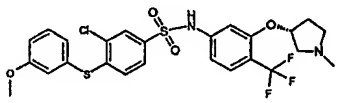
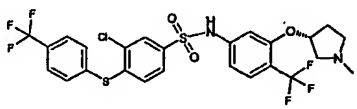
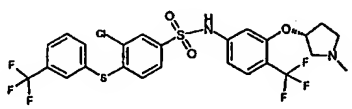
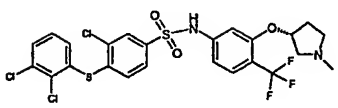
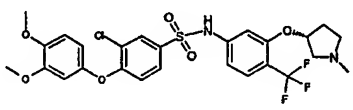
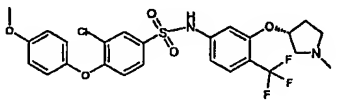
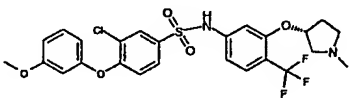
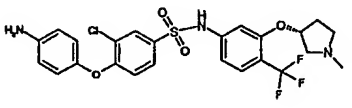
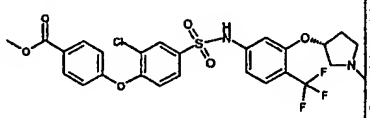
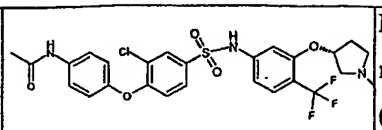
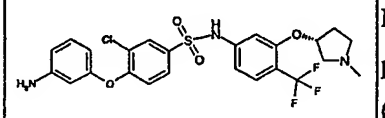
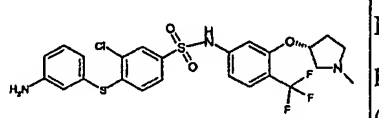
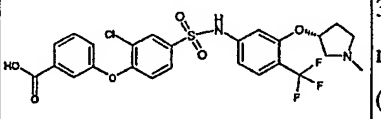
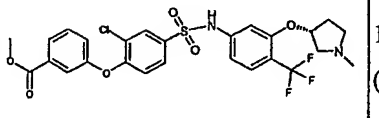
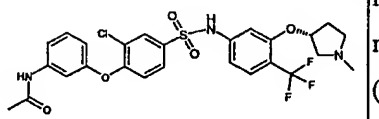
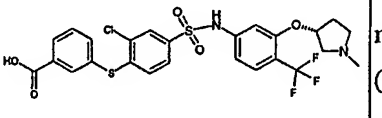
79		2-chloro-4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	611
80		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(4-fluorophenyl)thio]benzenesulfonamide	527
81		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide	577
82		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(methyloxy)phenyl]thio}benzenesulfonamide	539
83		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(3,5-dichlorophenyl)thio]benzenesulfonamide	543
84		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide	543

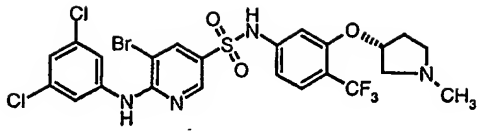
85		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(methyloxy)phenyl]thio}benzenesulfonamide	505
86		2-chloro-4-[(3-chloro-4-fluorophenyl)thio]-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	561
87		2-chloro-4-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	587
88		2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-phenoxybenzenesulfonamide	527
89		3-chloro-4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	603
90		3-chloro-4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	573
91		3-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide	611

92		3-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide	611
93		3-chloro-4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	612
94		3-chloro-4-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	587
95		3-chloro-4-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	557
96		3-chloro-4-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	557
97		4-(4-aminophenoxy)-3-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	542
98		methyl 4-[2-chloro-4-({[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenoxy]benzoate	585

99		N-{4-[2-chloro-4-({[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenoxy]phenyl}acetamide	584
100		4-[(3-aminophenyl)oxy]-3-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	542
101		4-[(3-aminophenyl)thio]-3-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	558
102		3-{[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]oxy}benzoic acid	571
103		methyl 3-{[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]oxy}benzoate	585
104		N-(3-{[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]oxy}phenyl)acetamide	584
105		3-{[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]thio}benzoic acid	587

Example 106

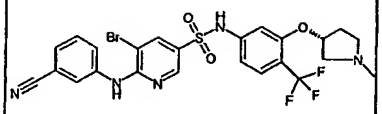
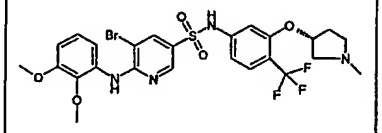
5-bromo-6-[(3,5-dichlorophenyl)amino]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]pyridine-3-sulfonamide



5-bromo-6-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-pyridinesulfonamide (33.4 mg, 0.065 mmol) was dissolved in 1 mL of DME and treated with 3,5-dichloroaniline (52.0 mg, 0.324 mmol) and 4M HCl in dioxane (0.035 mL, 0.140 mmol) and heated to 130 °C for 18 hours. At this time, an additional 0.1 mL of 4M HCl in dioxane was added and the reaction was maintained at 130 °C for an additional 18 hours. The reaction mixture was then allowed to cool to room temperature, was filtered, and purified by preparative HPLC (X-Terra Prep RP ODS-A, 30 × 75 mm, 25 mL/min, A: acetonitrile B: water, A: 5% to 65% during 15 min, UV detection at 214 nm) to give 7.6 mg (18%) of the title compound as a light tan solid. MS (ES) m/e 639 $[M+H]^+$

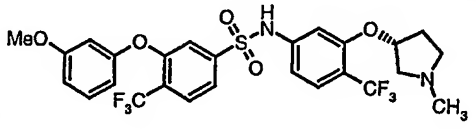
Examples 107-108

The following compounds were prepared according to a procedure similar to that described in Example 107, except that the appropriate aniline was substituted for 3,5-dichloroaniline:

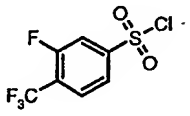
#	structure	name	m/z
107		5-bromo-6-[(3-cyanophenyl)amino]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-pyridinesulfonamide	596.0
108		6-{[2,3-bis(methyloxy)phenyl]amino}-5-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-pyridinesulfonamide	631.0

Example 109

3-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide

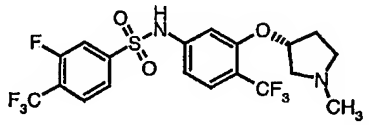


a) 3-fluoro-4-(trifluoromethyl)benzenesulfonyl chloride



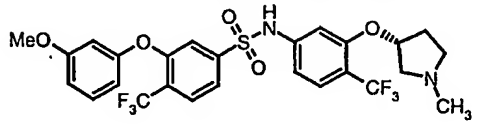
3-fluoro-4-(trifluoromethyl)aniline (3.0 g, 16.8 mmol) was dissolved in 6 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 3.30 mL, 25.3 mmol) and *tert*-butyl nitrite (2.96 mL, 25.3 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (2.50 g, 25.3 mmol) in 20 mL of acetonitrile at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 100 mL of an ice/water slurry. The product precipitated out of solution and the solid was dissolved in diethyl ether, dried over sodium sulfate, filtered, and concentrated to 4.31 g (97 %) of an amber oil which was used directly in the next step without further purification.

b) 3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide



A 25-mL round-bottom flask equipped with an argon inlet and a magnetic stirring bar was charged with 3.0 g (13.6 mmol) of Aniline A and 6 mL of anhydrous methylene chloride. The contents of the flask were stirred at room temperature until all of the solids were dissolved, and 2.2 mL of anhydrous pyridine was added. The solution was stirred for 60 sec before 4.31 mg (16.4 mmol) of 3-fluoro-4-(trifluoromethyl)benzenesulfonyl chloride was added and the resulting mixture was stirred and maintained at room temperature for 18 hours. The solvent was removed by rotary evaporation at reduced pressure and the crude oil was dissolved in DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A 50 x 20 mm, 20mL/min, A: acetonitrile B: water, 10 – 90% over 10 min, UV detection at 214 nm) to give 4.41 g (67%) of the title compound as a pale amber oil.

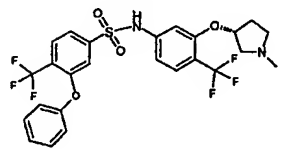
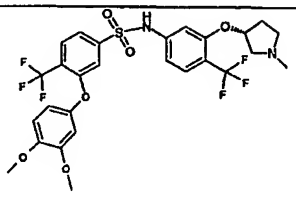
c) 3-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide

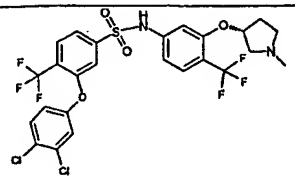
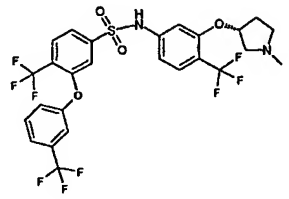
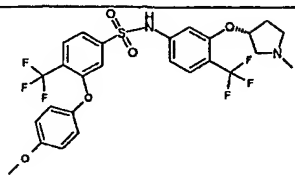


A microwave-safe vial, equipped with a magnetic stirring bar was charged with 12 mg (0.31mmol) of NaH (60% by weight) and 404 mg (1.24mmol) of Cs_2CO_3. A solution consisting of 38 mg (0.31 mmol) 3-methoxyphenol and 0.36 mL of anhydrous NMP was prepared separately and added dropwise to the microwave vial. The mixture was stirred for 30 min and then 146 mg (0.3 mmol) of 3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide dissolved in 1.86 mL of anhydrous NMP was delivered to the vial. The vial was capped and its contents were stirred vigorously for 5 min. Afterwards, the vial was heated to 200 °C for 7.5 min at the Normal Power level using the Emrys Optimizer Personal Chemistry Microwave Reactor. The reaction mixture was cooled to room temperature, filtered through a 0.2 um Acrodisk filter, and purified by preparative HPLC (YMC CombiPrep ODS-A 50 x 20 mm, 20mL/min, A: acetonitrile B: water, 10 – 90% over 10 min, UV detection at 214 nm) to give 77.5 mg (42%) of the title compound as a dark amber oil. MS (ES) m/e 591 [M+H]+

Examples 110-114

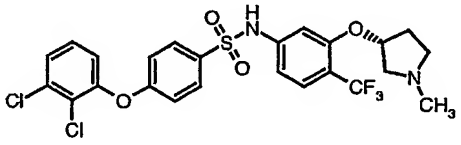
The following examples were prepared according to the representative procedure in Example 110 using the appropriate phenols and thiophenols in place of 3-methoxyphenol:

#	structure	name	m/z
110		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-3-phenoxy-4-(trifluoromethyl)benzenesulfonamide	561
111		3-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	621

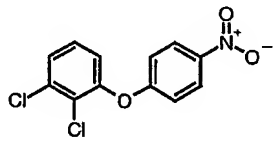
112		3-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	629
113		N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)-3-[3-(trifluoromethyl)phenoxy]benzenesulfonamide	629
114		3-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	591

Example 115

4-[(2,3-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide



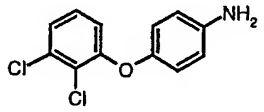
a) 1,2-dichloro-3-(4-nitrophenoxy)benzene



A 250-mL round-bottom flask equipped with an argon inlet and a magnetic stirring bar was charged with 368 mg (9.2 mmol) of NaH. A solution of 1.5 g (9.2 mmol) of 2,3-dichlorophenol dissolved in 12 mL of anhydrous DMSO was added dropwise to the flask at room temperature. The mixture was stirred for 15 minutes until the evolution of H_2 gas ceased. The mixture was diluted with 12 mL of DMSO and stirred for five minutes at room temperature before a solution of 0.925 mL (8.7 mmol) of 4-fluoro-nitrobenzene dissolved in 56.4 mL of anhydrous DMSO was added to the reaction mixture. The reaction mixture was heated to 95°C and maintained at that temperature for 4 h, after which time it was allowed to cool to room temperature and was quenched by pouring it into H_2O (375 mL) and brine (75 mL). The product was extracted from this aqueous mixture several times using ethyl acetate and the

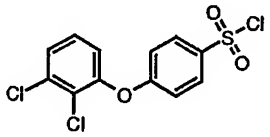
combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 2.24 g (85%) of the title compound which was used directly in the next step without further purification.

b) 4-[(2,3-dichlorophenyl)oxy]aniline



A 10-mL round bottom flask equipped with an argon inlet and a magnetic stirring bar was charged with 393 mg (7.04 mmol) of iron powder suspended in 3.36 ml of glacial acetic acid. This mixture was heated to 60°C and maintained at that temperature for 15 min with vigorous stirring. The reaction mixture was removed from heating while a solution of 500 mg (1.76 mmol) of 1,2-dichloro-3-(4-nitrophenoxy)benzene dissolved in 2 mL of glacial acetic acid was added and heating was then resumed at 80°C for 1 h. The reaction mixture was allowed to cool to room temperature and filtered through Celite. The filter cake was washed several times with MeOH and the combined filtrates were concentrated under reduced pressure to give a pale yellow oil, which was dissolved in 100 mL of ethyl acetate and washed several times with saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$, filtered, concentrated to an oil, and purified by silica gel chromatography (35 g Redisep column, silica, 40 um, 60 Å, 35 mL/min, A: hexanes, B: ethyl acetate, B: 0% for 20 min, 5% for 15 min, 50% for 20 min; detection at 214 nm) to give 400 mg (89%) of the title compound.

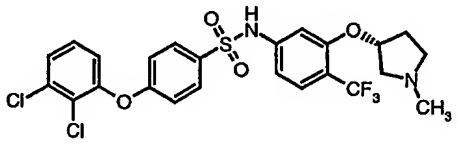
c) 4-[(2,3-dichlorophenyl)oxy]benzenesulfonyl chloride



A 10-mL round- bottom flask equipped with an argon inlet and magnetic stirring bar was charged with 200 mg (0.78 mmol) of 4-[(2,3-dichlorophenyl)oxy]aniline and 1 mL of anhydrous acetonitrile. The contents of the flask were stirred at room temperature until all of the solids were dissolved and 0.15 mL (1.17 mmol) of HBF_4 (48% in H2O) was added. The flask was placed in an ice bath and cooled to 0°C for 30min before 0.14 mL (1.17 mmol) of *t*-Butyl nitrite was delivered to the flask and maintained at 0°C for 1 h. In a separate flask, a suspension of CuCl (116 mg, 1.17 mmol) in 3 mL of acetonitrile was cooled to 0 °C and was saturated with sulfur dioxide gas by bubbling the gas through the suspension for 45 minutes.

After one hour, the solution of diazo compound was added dropwise to the suspension of CuCl at 0 °C and stirred for 10 minutes at 0°C and then allowed to warm to room temperature and stir for one hour. The reaction was quenched by pouring the mixture onto 60 mL of ice water. The solid which precipitated was recovered by filtration and washed with ice water. The solid was dissolved in diethyl ether, dried over $MgSO_4$, filtered, and concentrated to give 190 mg (80%) of the title compound as an amber oil which was used directly in the next step without further purification.

d) 4-[(2,3-dichlorophenyl)oxyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-

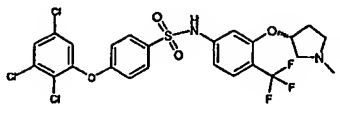


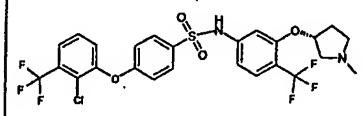
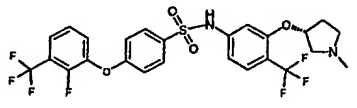
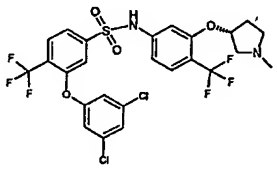
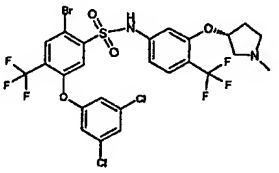
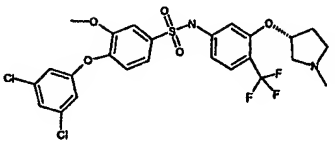
(trifluoromethyl)phenyl]benzenesulfonamide

A 5-mL round-bottom flask equipped with an argon inlet and a magnetic stirring bar was charged with 120 mg (0.46 mmol) of Aniline A and 4 mL of anhydrous methylene chloride. The contents of the flask were stirred at room temperature until all of the solids were dissolved, and 42.7 uL of anhydrous pyridine was added. The solution was stirred for 60 sec before 190 mg (0.56 mmol) of 4-[(2,3-dichlorophenyl)oxy]benzenesulfonyl chloride was added and the resulting mixture was stirred and maintained at room temperature for 18 hours. The solvent was removed by rotary evaporation and the crude oil was dissolved in DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A 50 x 20 mm, 20mL/min, A: acetonitrile B: water, 10 – 90% over 10 min, UV detection at 214 nm) to give 135.7 mg (53%) of the title compound as a pale amber oil. MS (ES) m/e 561 $[M+H]^+$

Examples 116-121

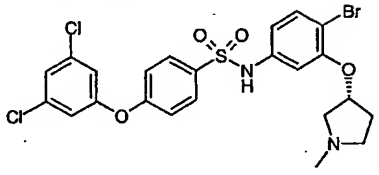
The following examples were prepared according to the representive procedure in Example 117 using the appropriate phenols in place of 2,3-dichlorophenol and the appropriate nitrobenzenes in place of 4-fluoronitrobenzene.

#	structure	name	m/z
116		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-[(2,3,5-trichlorophenyl)oxy]benzenesulfonamide	596

117		4-{[2-chloro-3-(trifluoromethyl)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	595
118		4-{[2-fluoro-3-(trifluoromethyl)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	579
119		3-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	629
120		2-bromo-5-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	708
121		4-(3,5-Dichlorophenoxy)-3-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	591

Example 122

N-(4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(3,5-



dichlorophenyl)oxy]benzenesulfonamide

Tribromoborane (25 g, 100 mmol) was added dropwise to a solution of 2-bromo-5-nitroanisole (7.94 g, 34.2 mmol) in methylene chloride (100 mL) at 0 °C. The solution was allowed to warm to room temperature and react for 16 h. The reaction was then quenched by the addition of methanol (20 mL) and stirred for 3 h. The solvent was removed under reduced pressure and the remaining residue purified by column chromatography (400 g silica gel 60, 230-400 mesh, 5-20% ethyl acetate/hexanes as eluent) to give 2-bromo-5-nitrophenol (6.2 g, 83%). MS (ES) m/e 217.6 $[M+H]^+$.

Diisopropyl azodicarboxylate (3.34 g, 16.5 mmol) was added dropwise to a solution of 2-bromo-5-nitrophenol (3.0 g, 13.8 mmol), (3*S*)-1-methyl-3-pyrrolidinol (1.4 g, 13.8 mmol), and triphenylphosphine (4.33 g, 16.5 mmol) in methylene chloride (100 mL). The reaction was maintained for 16 h at room temperature. The solvent was removed under reduced pressure and the remaining material purified by column chromatography (300 g silica gel 60, 230-400 mesh, 0-5% methanol/methylene chloride as eluent) to provide (3*R*)-3-[(2-bromo-5-nitrophenyl)oxy]-1-methylpyrrolidine (2.6 g, 63%). MS (ES) m/e 301.2 $[M+H]^+$.

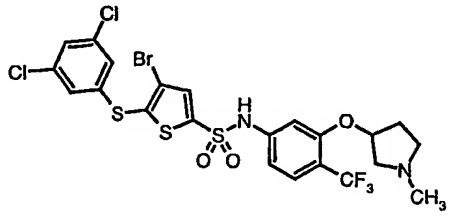
A mixture of iron (5 g) and iron (III) chloride (5 g) was added to a solution of (3*R*)-3-[(2-bromo-5-nitrophenyl)oxy]-1-methylpyrrolidine (2.2 g, 7.3 mmol) in acetic acid (15 mL) and water (5 mL). After stirring for 18 h at room temperature, the mixture was filtered and concentrated. The remaining residue was dissolved in aqueous hydrochloric acid (6 mL of a 2 M aqueous solution) and ethyl acetate (10 mL). The layers were separated and the organic layer discarded. The aqueous layer was concentrated to give 4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}aniline as a hydrochloride salt (2.2 g, 100%). MS (ES) m/e 271.2 $[M+H]^+$.

A solution of 4-[(3,5-dichlorophenyl)oxy]benzenesulfonyl chloride (56 mg, 0.17 mmol) in methylene chloride (0.5 mL) was added to a solution of 4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}aniline (50 mg, 0.18 mmol) and pyridine (3 mL) in methylene chloride (0.5 mL). The solution was maintained at room temperature for 15 h. The volatiles were removed

under reduced pressure and the remaining crude material was purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (37 mg, 30%) as a trifluoroacetate salt. MS (ES) m/e 571.2 $[M+H]^+$.

Example 123

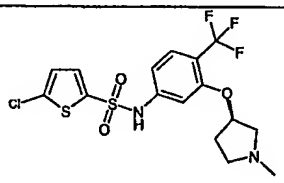
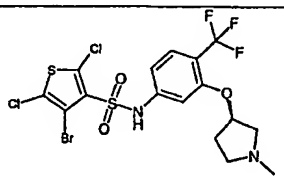
4-bromo-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-

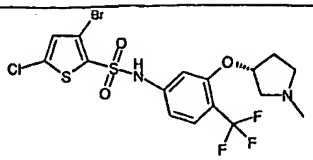
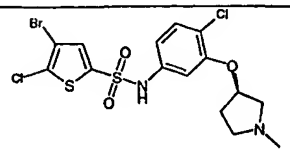
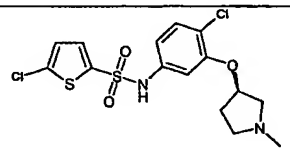


(trifluoromethyl)phenyl]-2-thiophenesulfonamide:

4-Bromo-5-chloro-thiophene-2-sulfonic acid [3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide (100 mg, 0.19 mmol) was added as a solid to a mixture of 3,5-dichlorothiophenol (38 mg, 0.21 mmol) and 1N NaOH solution (0.21 mL, 0.21 mmol) in DMF (1.5 mL) under argon with vigorous stirring. The reaction mixture was heated at 100°C for 6 h. The reaction mixture was allowed to cool to room temperature, filtered and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 10 to 90% over 10 min, UV detection at 214 nm) to give 94 mg (79 %) of the title compound as a white microcrystalline solid. MS (ES) m/e 661 $[M+H]^+$.

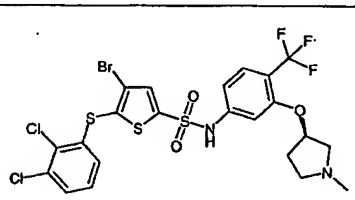
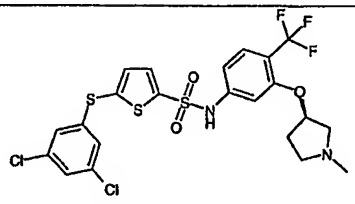
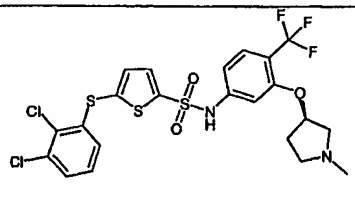
Chlorothiophene sulfonamides substituted for 4-Bromo-5-chloro-thiophene-2-sulfonic acid [3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide:

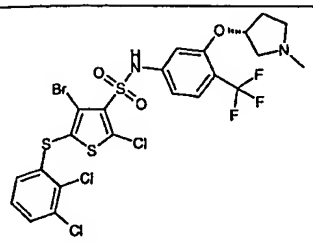
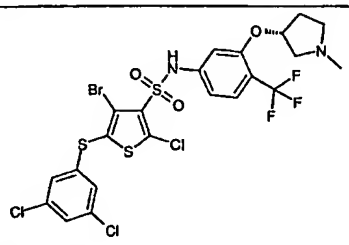
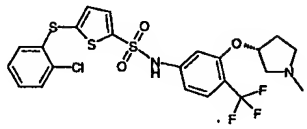
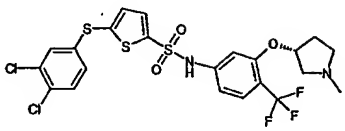
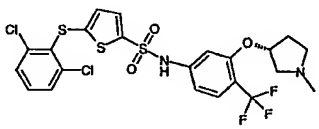
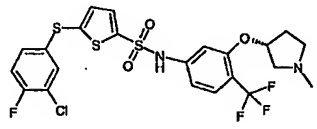
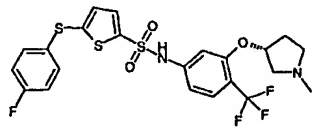
Chlorothiophenesulfonamide	name
	5-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide
	4-bromo-2,5-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide

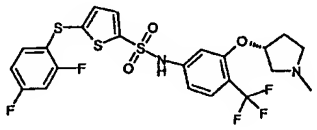
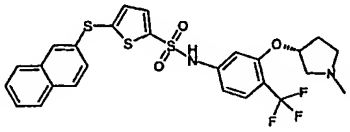
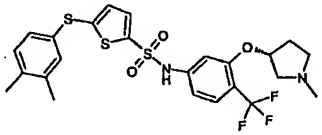
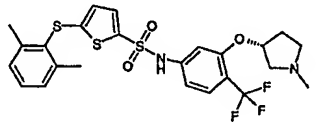
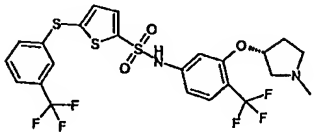
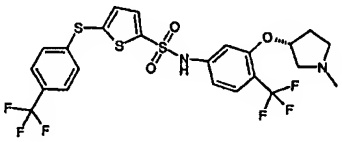
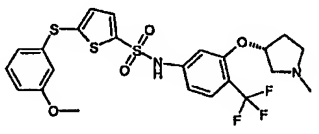
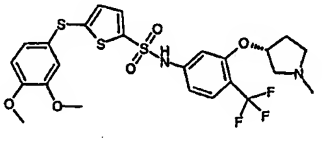
	3-bromo-5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide
	4-bromo-5-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-thiophenesulfonamide
	5-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-thiophenesulfonamide

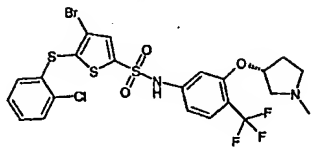
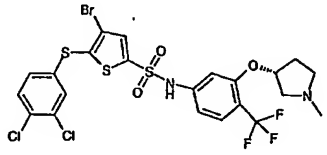
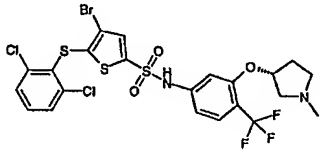
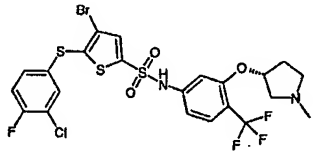
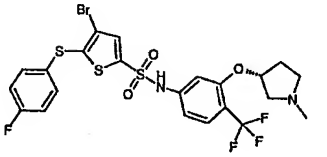
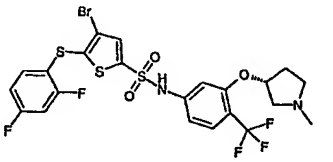
Examples 124-163

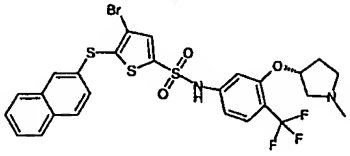
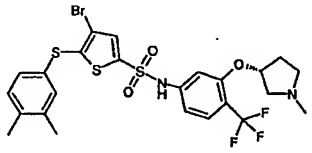
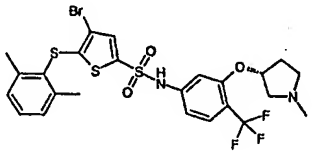
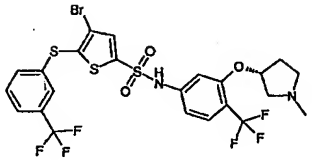
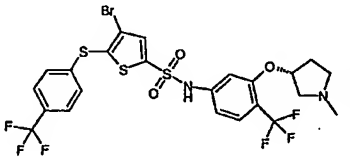
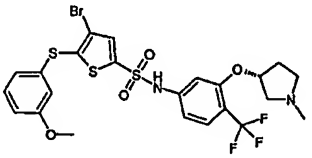
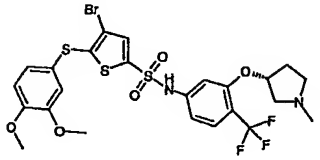
The following compounds were prepared according to a procedure similar to the one described in Example 123, except substituting the appropriate benzenethiol or alkanethiol for 3,5-dichlorothiophenol, and sometimes substituting the appropriate chloro-thiophene-sulfonamide from the table above for 4-Bromo-5-chloro-thiophene-2-sulfonic acid [3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide:

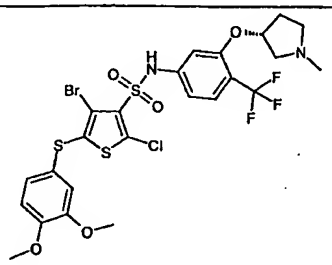
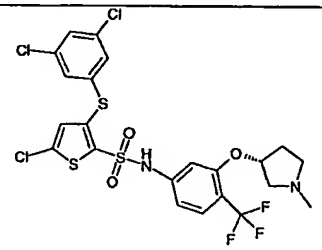
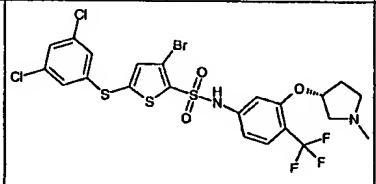
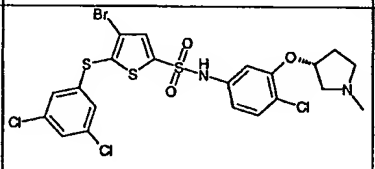
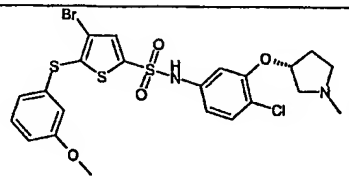
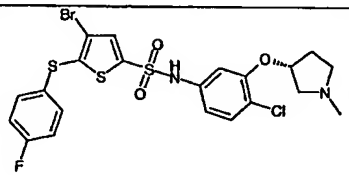
#	structure	name	m/z
124		4-bromo-5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	661
125		5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	583
126		5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	583

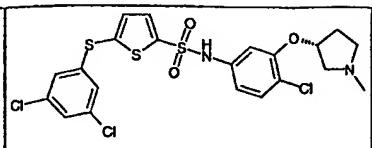
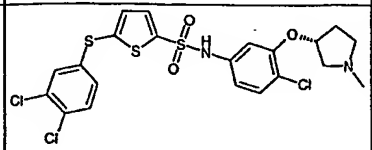
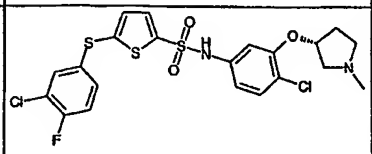
127		4-bromo-2-chloro-5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide	697
128		4-bromo-2-chloro-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide	697
129		5-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	549
130		5-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	583
131		5-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	583
132		5-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	567
133		5-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	533

134		5-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	551
135		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(2-naphthalenylthio)-2-thiophenesulfonamide	565
136		5-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	543
137		5-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	543
138		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide	583
139		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[4-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide	583
140		5-{[3-(methyloxy)phenyl]thio}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	545
141		5-{[3,4-bis(methyloxy)phenyl]thio}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-	575

		(trifluoromethyl)phenyl]-2-thiophenesulfonamide	
142		4-bromo-5-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	627
143		4-bromo-5-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	663
144		4-bromo-5-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	663
145		4-bromo-5-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	645
146		4-bromo-5-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	611
147		4-bromo-5-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	631

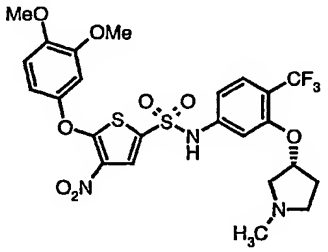
148		4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(2-naphthalenylthio)-2-thiophenesulfonamide	643
149		4-bromo-5-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	621
150		4-bromo-5-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	621
151		4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide	661
152		4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[4-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide	661
153		4-bromo-5-{[3-(methyloxy)phenyl]thio}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	623
154		5-{[3,4-bis(methyloxy)phenyl]thio}-4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-	653

		thiophenesulfonamide	
155		5-{[3,4-bis(methyloxy)phenyl]thio}-4-bromo-2-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide	687
156		5-chloro-3-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	616
157		3-bromo-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	661
158		4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(3,5-dichlorophenyl)thio]-2-thiophenesulfonamide	627
159		4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-{[3-(methyloxy)phenyl]thio}-2-thiophenesulfonamide	589
160		4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(4-fluorophenyl)thio]-2-thiophenesulfonamide	577

161		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(3,5-dichlorophenyl)thio]-2-thiophenesulfonamide	549
162		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(3,4-dichlorophenyl)thio]-2-thiophenesulfonamide	549
163		5-[(3-chloro-4-fluorophenyl)thio]-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-thiophenesulfonamide	533

Example 241

5-{[3,4-bis(methyloxy)phenyl]oxy}-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-



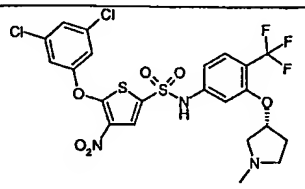
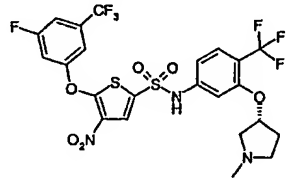
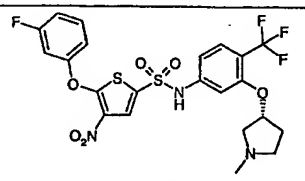
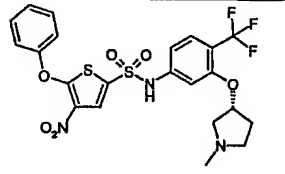
(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide

A solution of 5-chloro-4-nitro-2-thiophenesulfonyl chloride (1.0 g, 3.82 mmol) in methylene chloride (5 mL) was added to a solution of 3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)aniline (0.83 g, 3.18 mmol) and pyridine (0.76 g, 9.54 mmol) in methylene chloride (20 mL) at –78 °C. The solution was allowed to warm to room temperature and stir for 16 h. The volatiles were removed *in vacuo* and the remaining crude material purified by column chromatography (250 g silica gel 60, 230-400 mesh, 5-25% methanol/methylene chloride as eluent) to provide 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (500 mg, 33%). MS (ES) m/e 486.0 $[M+H]^+$.

To a mixture of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (100 mg, 0.21 mmol) and cesium carbonate (270 mg, 0.82 mmol) in dimethylformamide (5 mL) was added 3,4-dimethoxyphenol

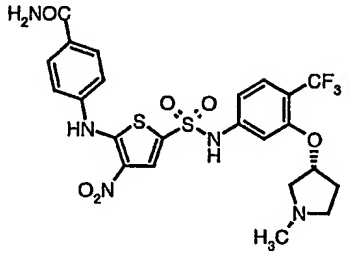
(40 mg, 0.25 mmol). The reaction was allowed to stir for 18 h. The mixture was filtered through a 0.45 µm fritted funnel and the remaining material purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroaceti acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (71 mg, 48%) as a trifluoroacetate salt. MS (ES) m/e 604.2 $[M+H]^+$.

The following examples were prepared according to the representative procedure in Example 164 using the appropriate phenols as starting material.

	structure	name	m/z
165		5-[(3,5-dichlorophenyl)oxy]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	612.0
166		5-{[3-fluoro-5-(trifluoromethyl)phenyl]oxy}-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	630.0
167		5-[(3-fluorophenyl)oxy]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	561.8
168		*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(phenyloxy)-2-thiophenesulfonamide	544.2

Example 169

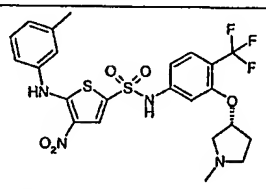
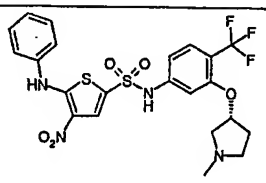
4-{[5-({[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-



nitro-2-thienyl]amino}benzamide

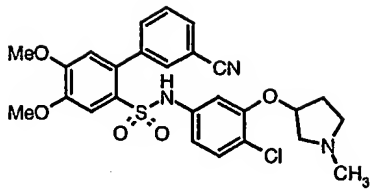
A solution of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (68 mg, 0.14 mmol) and 4-aminobenzamide (57 mg, 0.42 mmol) in dimethylformamide (1.5 mL) was heated in a Personal Chemistry microwave reactor at normal power for 600 sec at 200 °C. The mixture was filtered through a 0.45 μm fritted funnel and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (22 mg, 24%) as a trifluoroacetate salt. MS (ES) m/e 586.0 $[M+H]^+$.

The following examples were prepared in an analogous fashion to the representative procedure in Example 169 using the appropriate anilines as starting material.

	structure	name	m/z
170		5-[(3-methylphenyl)amino]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	557.0
171		*N*-[4-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-3-(trifluoromethyl)phenyl]-4-nitro-5-(phenylamino)-2-thiophenesulfonamide	543.2

Example 172

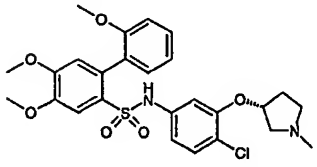
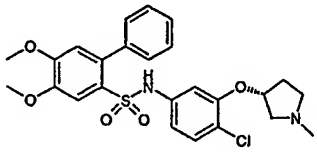
N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-cyano-4,5-bis(methyloxy)-2-biphenylsulfonamide

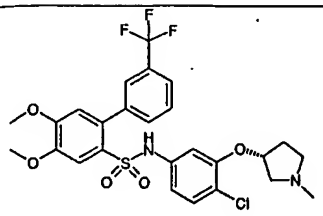
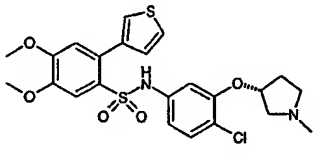
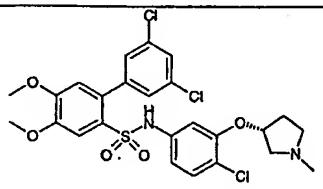
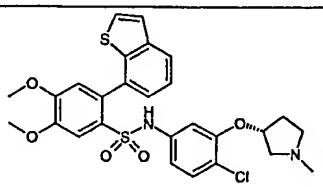
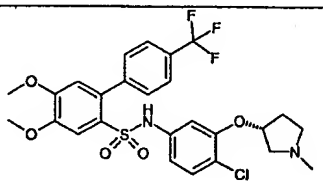
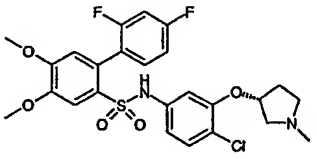
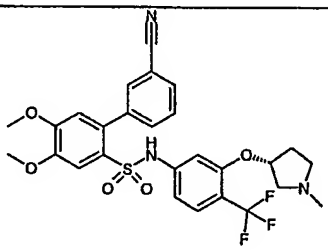


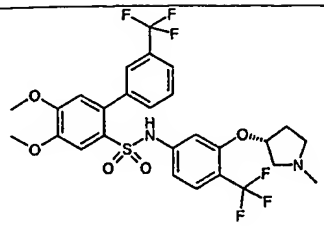
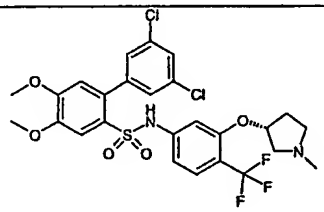
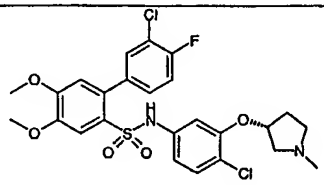
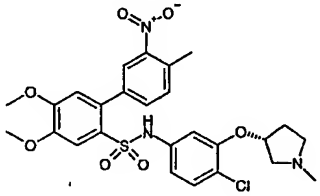
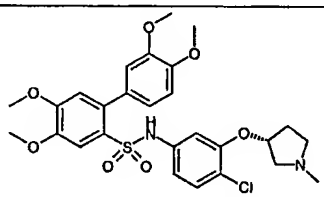
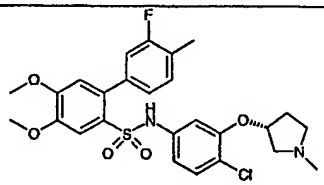
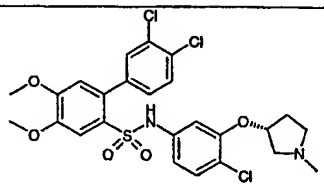
2-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide (150 mg, 0.297 mmol) was dissolved in 2 mL of anhydrous DMF and treated with [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (1:1) {Pd DPPF} (31 mg, 0.039 mmol), potassium carbonate (0.745 mL of a 2.0 M aqueous solution, 1.48 mmol), and (3-cyanophenyl)boronic acid (48.0 mg, 0.326 mmol). This suspension was stirred vigorously and heated to 170°C for 200 sec in a Personal Chemistry Microwave Reactor at the Normal power level. The reaction mixture was filtered through a 0.2 micron Acrodisk filter and purified by preparative HPLC (X-Terra Prep RP ODS-A, 30 × 75 mm, 25 mL/min, A: acetonitrile B: water, A: 5% to 65% during 15 min, UV detection at 214 nm) to give 38.1 mg (24%) of the title compound as a brown powder. MS (ES) m/e 528 $[M+H]^+$.

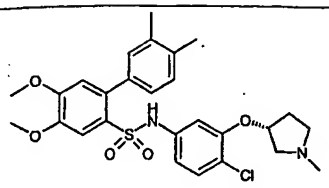
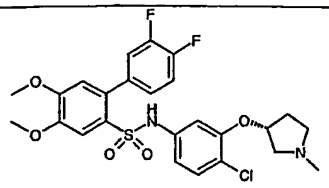
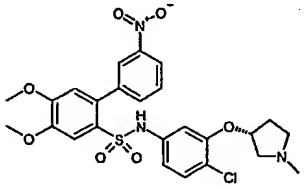
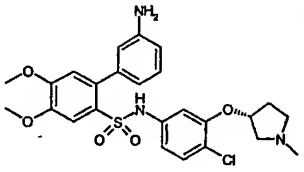
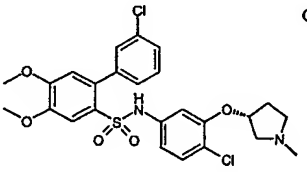
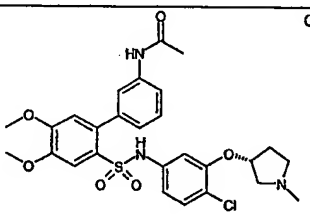
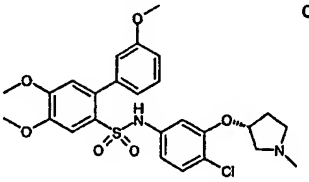
Example 173-225

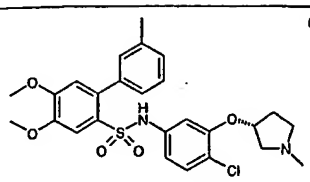
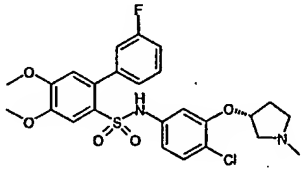
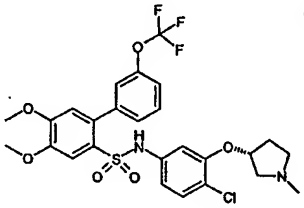
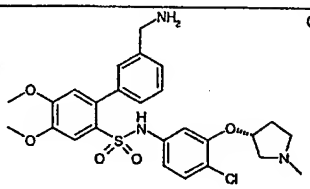
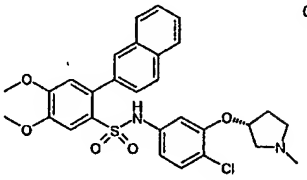
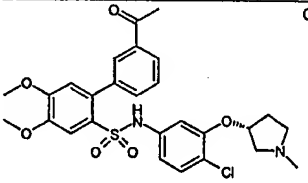
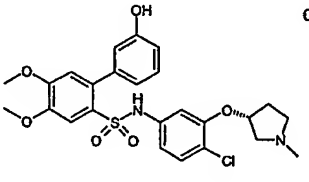
The following compounds were prepared according to the procedure described in Example 172, using the appropriate boronic acid in place of (3-cyanophenyl)boronic acid:

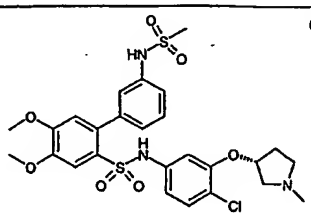
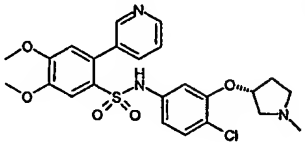
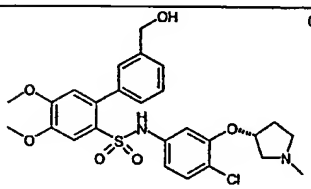
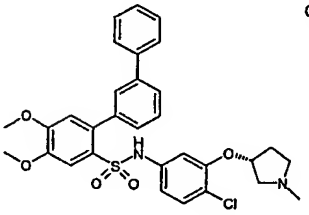
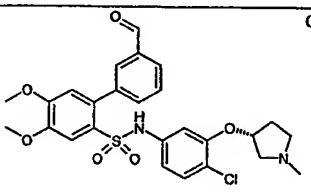
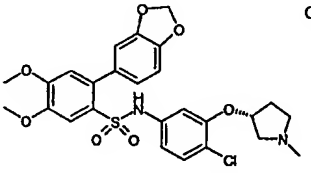
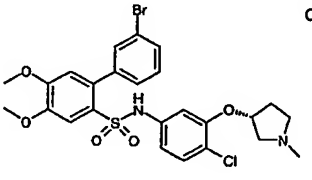
#	structure	name	m/z
173		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2',4,5-tris(methyloxy)-2-biphenylsulfonamide	533
174		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	503

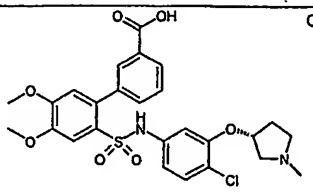
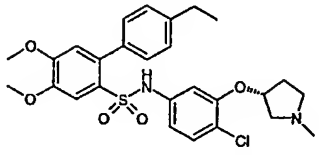
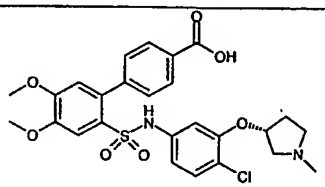
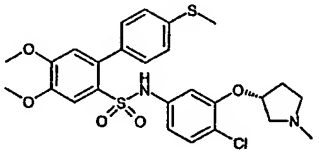
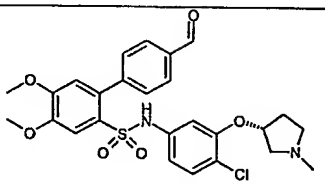
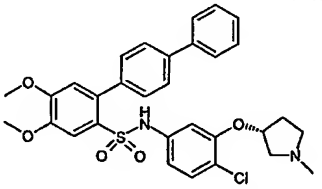
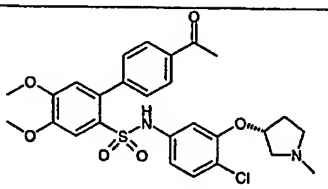
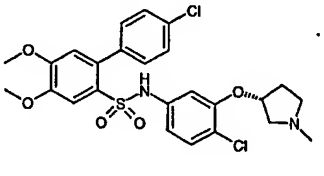
175		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-(trifluoromethyl)-2-biphenylsulfonamide	571
176		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(3-thienyl)benzenesulfonamide	509
177		3',5'-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	571
178		2-(1-benzothien-7-yl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide	559
179		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(trifluoromethyl)-2-biphenylsulfonamide	571
180		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2',4'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide	539
181		3'-cyano-4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-biphenylsulfonamide	562

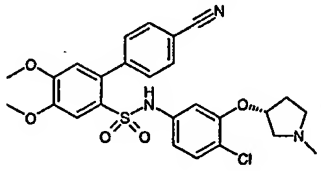
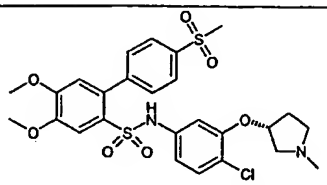
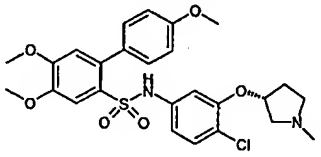
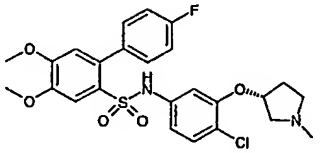
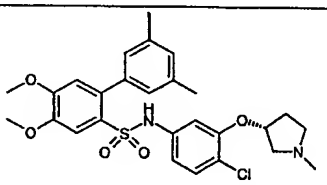
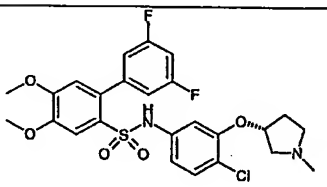
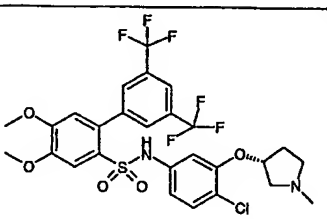
182		4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3'-(trifluoromethyl)-2-biphenylsulfonamide	605
183		3',5'-dichloro-4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-biphenylsulfonamide	605
184		3'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide	555
185		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-methyl-4,5-bis(methyloxy)-3'-nitro-2-biphenylsulfonamide	562
186		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4,4',5-tetrakis(methyloxy)-2-biphenylsulfonamide	563
187		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-fluoro-4'-methyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	535
188		3',4'-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	571

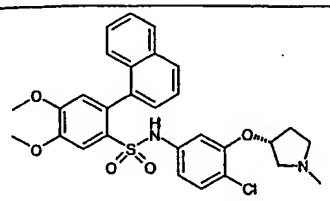
189		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4'-dimethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	530
190		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide	539
191	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-nitro-2-biphenylsulfonamide	548
192	 Chiral	3'-amino-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	518
193	 Chiral	3'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	537
194	 Chiral	N-[2'-{[(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)amino]sulfonyl}-4',5'-bis(methyloxy)-3-biphenylyl]acetamide	560
195	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4,5-tris(methyloxy)-2-biphenylsulfonamide	533

196	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-methyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	517
197	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide	521
198	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-[(trifluoromethyl)oxy]-2-biphenylsulfonamide	588
199	 Chiral	3'-(aminomethyl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	532
200	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(2-naphthalenyl)benzenesulfonamide	553
201	 Chiral	3'-acetyl-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	545
202	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-hydroxy-4,5-bis(methyloxy)-2-biphenylsulfonamide	519

203	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-[(methylsulfonyl)amino]-2-biphenylsulfonamide	597
204	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(3-pyridinyl)benzenesulfonamide	504
205	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-(hydroxymethyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	532
206	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-1,1':3',1"-terphenyl-2-sulfonamide	579
207	 Chiral	N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-formyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	531
208	 Chiral	2-(1,3-benzodioxol-5-yl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide	547
209	 Chiral	3'-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	579

210	 Chiral	2'-{[(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)amino]sulfonyl}-4',5'-bis(methyloxy)-3-biphenylcarboxylic acid	547
211		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-ethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	532
212		2'-{[(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)amino]sulfonyl}-4',5'-bis(methyloxy)-4-biphenylcarboxylic acid	547
213		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(methylthio)-2-biphenylsulfonamide	549
214		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-formyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	531
215		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-1,1':4',1"-terphenyl-2-sulfonamide	579
216		4'-acetyl-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	545
217		4'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide	537

218		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-cyano-4,5-bis(methyloxy)-2-biphenylsulfonamide	528
219		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(methylsulfonyl)-2-biphenylsulfonamide	582
220		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,4',5-tris(methyloxy)-2-biphenylsulfonamide	533
221		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide	521
222		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',5'-dimethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide	531
223		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',5'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide	539
224		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3',5'-bis(trifluoromethyl)-2-biphenylsulfonamide	639

225		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(1-naphthalenyl)benzenesulfonamide	553

EXAMPLE 226

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient	40 mg
(Cpd of Form. I)	
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

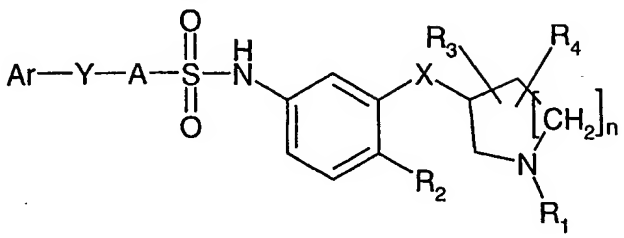
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

Ar is phenyl, pyridinyl, thienyl, furanyl, oxazoyl, pyrroyl, triazinyl, imidazoyl, pyrimidinyl, pyrazinyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl, naphthyl, quinolinyl, naphthyridinyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, azaspirononoyl, benothiophenyl, substituted or unsubstituted by one, two, three, or four of the following: halogen, CN, $S(O)_p(C_{1-6}$ alkyl), CF_3, OCF_3, SCF_3, C_{1-6} alkyl, Ph, OH, C_{1-6} alkoxy, COR_{11}, CO_2H, $CO_2(C_{1-6}$ alkyl), NR_5R_6, NR_5COR_{13}, $NR_5SO_2R_{13}$, $CONR_7R_8$, NO_2, C_{1-3} alkylenedioxy, $CH_2NR_7R_8$, or CH_2OR_{11};

A is phenyl, pyridyl, thienyl, furanyl, , oxazoyl, pyrroyl, triazinyl, imidazoyl, pyrimidinyl, pyrazinyl, N-phenylpyrroyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl, naphthyl, indoyl, quinolinyl, quinazolinyl, naphthyridinyl, benzothiophenyl, benzofuranyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, benzothiazoyl, benzoxazoyl, benzothiadiazoyl, benzoxadiazoyl, or benzimidazoyl, all of which may be substituted or unsubstituted by one, two, three or four halogens, C_{1-6} alkyl, C_{1-6} alkoxy, $CO_2(C_{1-6}$ alkyl), CN, CF_3 or NO_2 groups;

Y is O, NH, -C(O)-NH-CH_2-, -$S(O_p)$-, CH_2, or a bond;

R_1 is hydrogen, C_{1-6} alkyl, or -$(CH_2)_mR_{14}$;

R_2 is hydrogen, halogen, CF_3, CN, or C_{1-4} alkyl;

R_3 and R_4, are independently hydrogen, C_{1-6} alkyl, benzyl, -$C(R_{13})_2$-OR_{11}, -$COOR_{12}$, -$CONR_{11}$, or -$C(R_{13})_2$-$N(R_{11})_2$;

R_5, R_6, R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_{11} is hydrogen or C $_{1-6}$ alkyl;

R_{12} is C $_{1-6}$ alkyl;

R_{13} is independently hydrogen or C_{1-3}alkyl;

R_{14} is phenyl, OH, or -(C=O)C_{1-3}alkyl;

X is O, S, or CH_2;

n is 0, 1 or 2;

m is 1 or 2;

p is 0, 1, or 2

provided that when R_{14} is OH, m is 2;

also provided that when A is thienyl, and Ar is phenyl, pyrazoyl, napthyl, quinolinyl, benzodioxoyl, or benzofuranyl, Y is not a bond;

also provided that when A is phenyl and Y is a bond, Ar is attached ortho to SO_2-;

also provided that when Ar is phenyl, A is not pyridyl;

or a pharmaceutically acceptable salt thereof.

Ar is preferably phenyl, pyridinyl, thienyl, furanyl, oxazoyl, pyrroyl, imidazoyl, pyrimidinyl, pyrazoyl, substituted or unsubstituted by one, two, or three of the following: Cl, Br, F, CN, $S(O)_p(C_{1-3}$ alkyl), CF_3, C_{1-6} alkyl, OH, C_{1-3} alkoxy, COR_{11}, NR_5R_6, NR_5COR_{13}, $CONR_7R_8$, or NO_2.

A is preferably phenyl, pyridyl, thienyl, furanyl, , oxazoyl, imadazolyl, pyrimidinyl, pyrazoyl, thiazoyl, all of which may be substituted or unsubstituted by one or two Cl, Br, F, C_{1-3} alkyl, C_{1-3} alkoxy, CN, CF_3 or NO_2 groups.

Y is preferably O, NH, -$S(O_p)$-, CH_2, or a bond.

R_1 is preferably hydrogen or C_{1-3} alkyl.

R_2 is preferably hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl.

R_3 and R_4, are preferably independently hydrogen or C_{1-3} alkyl.

R_5, R_6, R_7, and R_8 are preferably independently hydrogen or C_{1-3} alkyl.

R_{11} is preferably hydrogen or C $_{1-3}$ alkyl.

R_{13} is preferably hydrogen or C_{1-3}alkyl.

X is preferably O.

n is preferably 1.

p is preferably 0, 1 or 2.

2. A compound of claim 1 wherein:

Ar is phenyl, pyridinyl, thienyl, furanyl, oxazoyl, pyrroyl, imidazoyl, pyrimidinyl, pyrazoyl, substituted or unsubstituted by one, two, or three of the following: Cl, Br, F, CN, $S(O)_p(C_{1-3}$ alkyl), CF_3, C_{1-6} alkyl, OH, C_{1-3} alkoxy, COR_{11}, NR_5R_6, NR_5COR_{13}, $CONR_7R_8$, or NO_2;

A is phenyl, pyridyl, thienyl, furanyl, , oxazoyl, imadazolyl, pyrimidinyl, pyrazoyl, thiazoyl, all of which may be substituted or unsubstituted by one or two Cl, Br, F, C_{1-3} alkyl, C_{1-3} alkoxy, CN, CF_3 or NO_2 groups;

Y is O, NH, $-S(O_p)-$, CH_2, or a bond;

R_1 is hydrogen or C_{1-3} alkyl;

R_2 is hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl;

R_3 and R_4, are independently hydrogen or C_{1-3} alkyl;

R_5, R_6, R_7, and R_8 are independently hydrogen or C_{1-3} alkyl;

R_{11} is hydrogen or C $_{1-3}$ alkyl;

R_{13} is hydrogen or C_{1-3}alkyl;

X is O;

n is 1; and

p is 0, 1 or 2.

3. A compound of Claim 1 chosen from:

4-(2-chlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

3-(3,5-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(phenylsulfonyl)-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(phenylsulfonyl)-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)-2-pyridinyl]sulfonyl}-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)-4-{[4-(trifluoromethyl)phenyl]oxy}benzenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(phenyloxy)-3-(trifluoromethyl)benzenesulfonamide;

4-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(2-naphthylthio)benzenesulfonamide;

2-chloro-4-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(3,4-dimethoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(4-fluorophenyl)thio]benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-{[3-(methyloxy)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(3-chloro-4-fluorophenyl)thio]-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide;

2-chloro-4-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-phenoxybenzenesulfonamide; MS (ES) m/e 527

3-chloro-4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide

3-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[4-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

3-chloro-4-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

3-chloro-4-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-{4-[2-chloro-4-({[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenoxy]phenyl}acetamide;

5-bromo-6-[(3,5-dichlorophenyl)amino]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]pyridine-3-sulfonamide;

6-{[2,3-bis(methyloxy)phenyl]amino}-5-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-pyridinesulfonamide;

3-(3,4-dichlorophenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)-3-[3-(trifluoromethyl)phenoxy]benzenesulfonamide;

4-{[2-chloro-3-(trifluoromethyl)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-{[2-fluoro-3-(trifluoromethyl)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

4-(3,5-Dichlorophenoxy)-3-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

4-bromo-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(2-naphthalenylthio)-2-thiophenesulfonamide;

5-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(2-naphthalenylthio)-2-thiophenesulfonamide;

4-bromo-5-[(3,4-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(2,6-dimethylphenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[3-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide;

5-{[3,4-bis(methyloxy)phenyl]thio}-4-bromo-2-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide;

3-bromo-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(3,5-dichlorophenyl)thio]-2-thiophenesulfonamide;

4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-[(4-fluorophenyl)thio]-2-thiophenesulfonamide;

5-[(3-chloro-4-fluorophenyl)thio]-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-thiophenesulfonamide;

5-{[3,4-bis(methyloxy)phenyl]oxy}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(phenyloxy)-2-thiophenesulfonamide;

4-{[5-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-nitro-2-thienyl]amino}benzamide;

5-[(3-methylphenyl)amino]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2',4,5-tris(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3',5'-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

2-(1-benzothien-7-yl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(trifluoromethyl)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2',4'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

2,5-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(3-thienyl)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4'-dimethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4'-difluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3'-amino-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-methyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-[(trifluoromethyl)oxy]-2-biphenylsulfonamide;

3'-(aminomethyl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(2-naphthalenyl)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-[(methylsulfonyl)amino]-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-1,1':3',1"-terphenyl-2-sulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-formyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

2-(1,3-benzodioxol-5-yl)-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-ethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(methylthio)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-formyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-1,1':4',1"-terphenyl-2-sulfonamide;

4'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-cyano-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-4'-(methylsulfonyl)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,4',5-tris(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',5'-dimethyl-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3',5'-bis(trifluoromethyl)-2-biphenylsulfonamide; and

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-(1-naphthalenyl)benzenesulfonamide.

4. A compound of claim 1 chosen from:

4-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(2-chlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide;

4-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(3,5-dichlorophenyl)thio] benzenesulfonamide;

4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(2,6-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]thio}benzenesulfonamide;

2-chloro-4-[(3-methoxyphenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

2-chloro-4-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

3-chloro-4-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

methyl 4-[2-chloro-4-({[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenoxy]benzoate;

methyl 3-{[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]oxy}benzoate;

3-(3-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

3-(3,4-dimethoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

3-(4-methoxyphenoxy)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

3-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

2-bromo-5-[(3,5-dichlorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide;

4-bromo-5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-2-chloro-5-[(2,3-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide;

4-bromo-2-chloro-5-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide;

5-[(3,4-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(2-chlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(3-chloro-4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(4-fluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-5-[(2,4-difluorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-{[4-(trifluoromethyl)phenyl]thio}-2-thiophenesulfonamide;

4-bromo-5-{[3-(methyloxy)phenyl]thio}-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-{[3,4-bis(methyloxy)phenyl]thio}-4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-chloro-3-[(3,5-dichlorophenyl)thio]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-[(3-fluorophenyl)oxy]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide;

N-[4-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-3-(trifluoromethyl)phenyl]-4-nitro-5-(phenylamino)-2-thiophenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3'-cyano-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-(trifluoromethyl)-2-biphenylsulfonamide;

3'-cyano-4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-biphenylsulfonamide;

4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3'-(trifluoromethyl)-2-biphenylsulfonamide;;

3',5'-dichloro-4,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-biphenylsulfonamide;

3'-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-fluoro-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4'-methyl-4,5-bis(methyloxy)-3'-nitro-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4,4',5-tetrakis(methyloxy)-2-biphenylsulfonamide;

3',4'-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-3'-nitro-2-biphenylsulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3',4,5-tris(methyloxy)-2-biphenylsulfonamide;

3'-acetyl-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide;

3'-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide; and

4'-acetyl-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)-2-biphenylsulfonamide.

5. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

6. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

7. A method according to Claim 6 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/35351

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : CO7D 207/00, 401/00; A61K 31/40, 31/44
US CL : 548/541; 546/278.;514/424, 340
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/541; 546/278.;514/424, 340

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,511,989 B2 (HEITSCH et al) 28 January 2003 .	1-7
A	US 6,686, 382 B2 (WU et al) 03 February 2004.	1-7
A	US 6699, 884 B2 (BROWN et al) 02 March 2004.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
	08 APR 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Deborah C Lambkin
Telephone No. 703-308-1235